REMARKS

1. Overview of Amendment

Claims 1-2, 7-9, 11-16, 18, 24, 32, 34 and 36-41 are pending in the present application. Claims 24, 32, 34 and 36-41 are withdrawn. Claims 1-2, 7-9, 11-16 and 18 are under consideration.

For the purpose of indicating proper support reference is made to the application published as WO 2005/073367.

Original claim 1 referred to production of a "recombinant arylsulfatase A" without any further structural characterization. It is evident that this term was intended to cover mutants, including fragments (truncation mutants) and substitution mutants, of human arylsulfatase A (ASA) by virtue of the dependency of claims 2 and 7 on claim 1.

The original claims 2 and 7 required that the mammalian cell comprise a nucleotide sequence that encoded (a) SEQ ID NOs:2 (claim 2) or 3 (claim 7); (b) an "enzymatically equivalent" fragment ("portion") of (a), or (c) an "enzymatically equivalent" mutant ("analogue") at least 75% identical to (a) or (b).

Page 8, lines 5-9 states:

> "an example of an enzymatically equivalent analogue of the enzyme could be a fusion protein which includes the catalytic site of the enzyme in a functional form, but it can also be a homologous variant of the enzyme derived from another species. Also, completely synthetic molecules, which mimic the specific enzymatic activity of the relevant enzyme, would also constitute "enzymatic equivalent analogues".

Applicants thus contemplated the possibility of a fusion protein. There is further discussion of possible fused entities at P8, L36 to P11, L14.

Claim 1 has been amended to require that the mammalian cell comprise a nucleotide sequence that encodes (a) SEQ ID NOS: 2 or 4, or (b) a mutant sequence at least 95% identical to (a), the mutant sequence having arylsulfatase A activity.

SEQ ID NO:2 is the full-length human ASA (507 AAs). SEQ ID

NO:4 is mature human ASA (489 AAs). Basis for "at least 95%" is at P14, L4-7 and P15, L23-25.

Mature human ASA is actually SEQ ID NO:3, in which the Cys-69 of SID2 (Cys-51 of SID 4) is converted to formyl glycine, see P15, L5-12. Claim 1 does not directly recite SEQ ID NO:3 because the formylglycine is not "encoded" by the nucleotide sequence, formylglycine not being one of the twenty genetically encoded amino acids. However, the produced arylsulfatase that is subsequently purified may, and in a preferred embodiment is, SEQ ID NO: 3.

It should be appreciated that since the expression is in a mammalian cell, if the mammalian cell comprises a nucleotide sequence that encodes SEQ ID NO:2, it will be processed by the cell to remove the 18 aa signal peptide (P2, L12-19), resulting in SEQ ID NO:4, and to post-translationally modify the Cys-69 (mASA Cys-51) to formlylglycine, resulting in SEQ ID NO: 3 (the active species). With SEQ ID NO:2 expressed, there will also be N-glycosylation and phosphorylation, see P11, L33-39.

The mammalian cell may alternatively comprise SEQ ID NO:4, joined to some other signal peptide that is recognized by the mammalian cell and thus cleaved off when the polypeptide is secreted.

The other amendments to claim 1 are of a minor character. Basis for reciting "<u>continuously</u> culturing..." in step (i) is in the preamble recitation of "continuous cell culture system". The amendment is introduced to avoid any issue as to whether a preamble recitation counts as a limitation.

Basis for the amendment "a cation <u>exchange</u> chromatography resin or membrane" may be found on p. 27, lines 37-38. Basis for the amendment "and/or affinity chromatography resin" may be found on page 24, lines 37-38. The amendment "exchange ~~chromatography~~" is to be interpreted merely as a correction of an obvious error.

Claim 11 has been amended so step vi) permits inactivating

virus with a virus inactivating agent, cp. original claim 18 and page 26, lines 35-37. Conforming amendments have been made to claim 18.

New claim 42, regarding the duration of continuous culturing, is based on P17, L1-4.

New claim 43, regarding the specific activity of the mutant, is based on P13, L21-29 and original claims 21 and 41.

New claims 44-47, reciting more stringent percentage identity limitations (at least 96, 97, 98 or 99%, respectively), are based on P14, L4-7 and P15, L23-25. New claim 48 requires that the encoded polypeptide comprises SEQ ID NOs:2 or 4, and 49 that the produced arylsulfatase A consists of SEQ ID NO:3 (cp. original claim 6). New claim 50 uses "consists" rather than "comprises" and thus effectively excludes fusion proteins.

New claim 51 reciting the Cys-51/Cys-69, is based on P2, L21-36 and P15, L5-12, and original claim 6. New claims 52-55, addressing the nearby residues, are based on P29, L30-36.

New claims 56-59, relating to glycosylation, are based on P11, L33-39.

Withdrawn claims 24, 32, 34 and 36-41 have been cancelled.

2. Claim Objections (OA p. 3)

Claims 1 and 18 have been amended so as to overcome the Examiners objections regarding the terms "rhASA", "arylsulphatase" and "Ii".

The missing conjunctions have been supplied for claims 1, 2, 7 and 11.

3. Indefiniteness Issues - 35 USC § 112 ¶2 (OA p. 4)

Claim 18 has been rejected under 35 U.S.C. 112, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Base claim 11 has been amended to recite, in the viral

filtration step, "and/or inactivating virus in said fractions with a virus-inactivating agent". Claim 18 in turn is amended to simply state the agent is a detergent with basis at P27, L1-17. For basis, see P26, L35-37.

4. Written Description Issues 35 USC 112 ¶1 (OA p. 4-8)

Claims 1-2, 7-9, 11-16 and 18 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The Examiner has interpreted the claims as encompassing production of "any or all recombinant arylsulfatase A, including any or all mutants, variants or fragments thereof, and any polypeptides comprising a portion of SEQ ID NO:2 or 3 (as little as two amino acids), wherein said polypeptides have arylsulfatase A activity. Therefore, says the examiner, the claims are drawn to a method of producing a genus of polypeptides having arylsulfatase activity but having unknown structure".

Even if this were an apt interpretation of claim 1, it's not clear to applicant why the examiner did not separately analyze claims 2 and 7, which were clearly limited to cells comprising nucleotide sequences encoding SEQ ID NO: 2 and 3, enzymatically active fragments of 2 and 3, and enzymatically active mutants at least 75% identical to SEQ ID NOS: 2 and 3 or the aforementioned enzymatically active fragments thereof.

In any event, claim 1 has been amended to require that the mammalian cells comprise a nucleotide sequence that encodes a polypeptide comprising (1) one of SEQ ID NOs:2-4, or (2) a mutant of (1) that is at least **95%** identical to (1) and has (or is processed by the cell into a product that has) arylsulfatase A activity.

The examiner conceded that even the claim as previously examined, and with the examiner's exceedingly expansive interpretation (does the examiner really believe that any dipeptide has arylsulfatase A activity?), is supported by two

disclosed species, SEQ ID NOs:2 and 3.[1]

The issue is therefore whether these two species, or at least SEQ ID NO:3, is/are representative of the claimed genus.

The examiner characterized the previously claimed genus as one embracing "widely variant species". However, that can hardly be considered true of the claims as amended, which include a requirement of at least 95% identity.

We respectfully direct the Examiner's attention to the PTO's Written Description Training Materials (Revision 1; March 25, 2008). The WDTM distinguishes between percentage identity claims which contain activity limitations, and those without. Claim 1 requires that the mutant have arylsulfatase A activity, which is an activity limitation.

The relevant WDTM analysis is of Example 10, model claim 3, Example 11A, model claim 2, and Example 11B, model claim 2.

Example 10 model claim 3 combined a 95% identity with an activity limitation. The analysis of WDTM Example 10 model claim 3 assumed that (1) there was "no teaching in the specification regarding which 5% of the structure can be varied while retaining the ability of the protein to catalyze the reaction A→B", and (2) "there is no art-recognized correlation between any structure (other than SEQ ID NO:3) and the activity of catalyzing A→B, based on which those of ordinary skill in the art could predict which amino acids can vary from SEQ ID NO:3 without losing catalytic activity". On these facts, it held lack of WD.

Examples 11A and B, model claim 2, combined an **85%** identity limitation with an activity limitation. The analysis was elaborated upon with respect to model claim 2 of Examples 11A and 11B. In Ex. 11A, the PTO assumed that an "art-recognized structure function correlation" was not present, and in 11B, that it was. As a result it found WD satisfied in 11B but not in 11A.

In the analysis of Ex. 11A, the PTO began by assuming that

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[1] As noted above, SEQ ID NO:2 is actually the precursor to SEQ ID NO:3, which is mature ASA.

there was no significant sequence identity between the recited polypeptide and any known polypeptide, or disclosure of any additional activity polypeptides in the specification (page 37). It conceded that the skilled worker was aware of "amino acid substitution exchange groups" and that substitutions within the exchange group would be expected to conserve the overall tertiary structure[2]. However, it declined to consider this knowledge sufficient to assure conservation of function (pp. 38-39). (We wish to note that in the studies which were used to define the exchange groups, the standard was in fact conservation of function, not 3D structure, because 3D structure data was available for fewer protein families.)

In Ex. 11B, the PTO assumed that there was "data from deletion studies that identified two domains as critical to activity Y, i.e., a binding domain and a catalytic domain". It also assumed that the applicants disclosed limiting mutations within these domains to conservative substitutions (per the aforementioned exchange groups), and permitting non-conservative substitutions outside those domains. Thus, "conservative substitutions" teachings were deemed relevant to an "activity" claim if coupled with some sort of "active site" teaching. The WDTM made it clear that it was not necessary that all of the suggested mutations in fact result in an active mutant, just that the art would expect that "many" of them would (see paragraph bridging pp. 41-42).

Here, human ASA (SEQ ID NO:3) is not the only known sulfatases, or arylsulfatases.

Human arylsulfatase A precursor is 507 aa and consists of an 18 aa signal peptide, and 489 aa mature sequence. See P2, L12-19. The specification explicitly identifies the Cys-51 (more precisely, fGly-5) of mature ASA as being part of the active site. Thus, at P2, L21-36 it states:

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[2] At least if % identity was at least 50%, see WDTM p. 38.

> A protein modification has been identified in two eukaryotic sulfatases (ASA and arylsulfatase B (ASB)) and for one from the green alga *Volvox carteri* (Schmidt B et al. Cell. 1995, 82, 271-278, Selmer T et al. Eur J Biochem. 1996, 238, 341-345). This modification leads to the conversion of a cysteine residue, which is conserved among the known sulfatases, into a 2-amino-3-oxopropionic acid residue (Schmidt B et al. Cell. 1995, 82, 271-278). The novel amino acid derivative is also recognised as C_{α}-formylglycin (Fgly). In ASA and ASB derived from MSD cells, the Cys-69 residue is retained. Consequently, it is proposed that the conversion of the Cys-69 to Fgly-69 is required for generating catalytically active ASA and ASB, and that deficiency of this protein modification is the cause of MSD. Cys-69 is referred to the precursor ASA which has an 18 residue signal peptide. In the mASA the mentioned cysteine residue is Cys-51. Further investigations have shown that a linear sequence of 16 residues surrounding the Cys-51 in the mASA is sufficient to direct the conversion and that the protein modification occurs after or at a late stage of co-translational protein translocation into the endoplasmic reticulum when the polypeptide is not yet folded to its native structure (Dierks T et al. Proc Natl Acad Sci. 1997, 94, 11963-1196, Wittke, D. et al. (2004), *Acta Neurophathol.* (Berl.), 108, 261-271).

Moreover, P15, L5-12 teaches

> As explained the post translational modification of the cysteine resifue in position 51 in the mature human arylsulfatase A is critical for the activity of the enzyme. Accordingly, in a preferred embodiment of the present invention production of the arylsulfatase A or its equivalent occurs at a rate and under conditions, which result in a product comprising an isoform of the enzyme in which the amino acid corresponding to Cys-69 in SEQ ID NO: 2 is converted to Formylglycine, corresponding to Fgly-51 in SEQ IDN O: 3. SEQ ID NO: 4 represents mature human arylsulfatase A after cleavage of the 18 amino acid signal peptide but prior to

modification of C-51.

Later, P29, L30-36 teaches

> I may be an advantage that the sequence of amino acid residues surrounding the Cys-51 is identical or has a high degree of sequence identity to the corresponding sequence in SEQ ID NO: 3. Thus, it may be preferred that a linear sequence of 20 amino acids, such as 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5 or 4 amino acid residues surrounding the Cys-51 in the arylsulfatase A is identical ro at least 90% identical, such as 95%, 96%, 97%, 98%, or 99% identical to the corresponding sequence in SEQ ID NO: 3.

Moreover, there are known structure-activity correlations for arylsulfatases and, more generally, sulfatases. (Citations are to art made of record by the concurrently filed IDS #3.)

Lee and Van Ettev (1975)(Ref. CF) concluded on the basis of the pH dependence of inactivation of ASA by diethyl pyrocarbonate, and reactivation of ASA by hydroxylamine, that at least one histidine was part of the active site of ASA.

James (1979)(Ref. CE) reported on the basis of the dose dependence of 2,3-butanedione inactivation that at least one arginine was also part of the active site.

Schuchman (1990)(Ref. CK) reported the cloning and sequencing of human arylsulfatase B and compared its sequence with that of human arylsulfatase A and C (Fig. 4). Schuchman noted that the sequence similarity was primarily in the N-terminal region, particularly ASB (full-length) residues 40-150. Particular attention was called to the conserved sequences ADDLG, LCTPSR and GKWHLG ([page 157, col. 1).

Peters (1990)(Ref. CH) compared, not only human ASA, ASB and ASC, but also sea urchin arylsulfatase, human steroid sulfatase, and human glucosamine-6-sulfatase (Fig. 6). Peters commented that the highest degree of homology was in the N-terminal third of the four complete mature peptides and included conserved five

(CTPSR) and six (GKWHLG) amino acid sequences. Peters noted that the box of six contained a histidine, and the box of five contained an arginine, with 2 more completely conserved arginines in the immediate vicinity.

Franco (1995)(Ref. CB) added comparisons with human arylsulfatases D, E and F (Fig. 2). All three feature CTPSR, and D and E present GKWHLG.

Bond (1996)(Ref. CA) reported the determination of the 3D structure of human arylsulfatase B (N-acetylgalactosamine-4-sulfatase). Bond compared its sequence to that of, inter alia, ASA, and located the active site as clustered about his sulfatase's Cys-91. This corresponds to the aforementioned CTPSR of ASA. The conserved residues lining the active site-pocket were said to include Arg-95 (the Arg of CTPSR) and His-147 (corresponding to the His of ASA's GKWHLG).

Lukatella (1998)(Ref. AX, IDS #2) reported the determination of the 3D structure of human arylsulfatase A. It notes the "critical role" of FGly69 (this is the genetically encoded Cys69) and says that it lies at the bottom of a positively charged cavity. The cavity is said to be formed by Asp281, Asn282, Asp29, Asp30, His229, Lys123, His125, Ser150, Lys302 and Arg73 (page 3659, bottom of col. 2). Asp29, Asp30, Asp281, FGly69 and Asn282 are said to be part of a metal (Mg++) binding site, too. Lukatella notes (3661 top col. 1) that "of the nine human sulfatases with known sequence, the aspartates (29, 30 and 281) coordinating to magnesium and the positively charged amino acids Arg73, Lys123 and Lys302 as well as His125 and His229 are strictly conserved." Lukatella also discusses the residues involved in regulation of dimer-octamer association (3662 col. 2)(e.g., Glu424) and compares ASA with other sulfatases (3663).

Gieselmann (1989), Ricketts et al. (1998) and Perusi (1997) show that certain naturally occurring human ASA mutants (variants) retain ASA activity.

Gieselmann (1989)(Ref. CC) disclose two mutations associated

with ARSA pseudodeficiency in which heterozygous and homozygous individuals carrying the mutations are healthy. One mutation alters an N-glycosylation site (N350S) the other is in the first polyadenylation site (1524+95A→G). An individual may carry one or both mutations on each allele.

Furthermore a number (≥5) of polymorphisms (single nucleotide changes), that results in no effect on enzyme activity have been reported in the literature.

Ricketts (1998)(Ref. CJ) discloses that the mutation R496H of ARSA does not negatively influence the activity of ARSA.

Perusi (1997)(Ref. CG) discloses a novel mutation, which in 1997, represented the fifth non-patogenic polymorphism in the coding sequence of the ASA gene. In the introduction it is stated that four ARSA gene polymorphisms previously have been identified, that are not associated with a decrease in enzyme activity, and are also found in healthy individuals. Three of these four polymorphisms result in an amino acid substitution with no pathologic effect and the fourth is located within intron 7.

Thus, the data presented above demonstrate recognition of some tolerance towards sequence modification. It is possible that more active variants exist since a population-based study in healthy individuals has not been done to determine additional silent mutations in ARSA.

Should the examiner not be persuaded that amended claim 1 satisfies the written description requirement, separate consideration should be given to new claims 43-59.

5. Enablement Issues (OA p. 8-12)

The Examiner concedes enablement for arylsulfatase A comprising SID 2 or 3, but states that there is a lack of predictability in the art with respect to the tolerance for sequence modification.

While the issue for written description was whether the completely identified species were "representative" of the claimed genera, and the issue for enablement purposes is whether it would require undue experimentation to identify operative species within the claimed genera, on a practical level these are closely intertwined.

A species is "representative" of the claimed genus if the art would expect most of the untested members of the genus to have properties similar to that of the lead species. Such an expectation would be equally relevant in an enablement context as it would suggest that it would not require undue experimentation to identify additional operative species and that the frequency of inoperative species would be low.

However, in enablement analysis, it is not necessary that such a priori expectation exist. If screening of members of the genus is easy, and so the experimentation required isn't "undue", a high frequency of failures might be tolerated. See Ex Parte Chen, 61 SPQ2d 1025 (BPAI 2000) (success rate of integration of transgene 1%; "the number emphasized by the Examiner would reasonably appear to reflect the need for a repetitive procedure, rather than undue experimentation"). That is particular true if the claim explicitly excludes inoperative species, see Ex parte Mark, 12 USPQ2d 1904 (BPAI 1989).

We now conduct a *Wands* analysis.

(1) nature of the invention

The invention relates to the purification of a recombinant protein.

(2) breadth of claims

The claims are limited to species encoding arylsulfatases highly similar (at least 95% identical) to the admittedly enabled species. Claims reciting just 80% identity, and supported by a single example, were held to be enabled in Ex parte Kubin, 83

USPQ2d 140 (BPAI 2007). The number of species putatively covered by the claim is not particularly relevant, see In re Angstadt, 190 USPQ 214, 218 (CCPA 1976).

(3) state of the prior art

The 3D structure of human ASA and ASB are known, and the sequence of human ASA has been compared that of many other sufatases. See the discussion of WD issues for particulars.

(4) relative skill of those in the art

The skill of workers in the molecular biology art is considered to be high, e.g., post-doc level.

(5) predictability or unpredictability of the art

While the effect of a mutation is not completely predictable, there are certain general expectations, e.g., mutation in the known active site is more likely to affect activity than mutation elsewhere; replacement of a residue with one similar in charge, hydrophilicity and size (a "conservative substitution") is more likely to be tolerated than replacement with a dissimilar one; the effects of mutation are usually additive; and mutants with a higher sequence identity to the original polypeptide are more likely to be active than those with a lower identity.

(6) the amount of direction or guidance presented

This was already analyzed in the WD context. But particular attention was drawn to Cys69 of SID 2, and to the glycosylation sites.

(7) presence or absence of working examples

See examples.

(8) quantity of experimentation necessary

Molecular biology is not a "fledgling art". We have had

over two decades of experience in mutating proteins.

The general tolerance of the various positions of human mASA to mutation can quickly be determined by alanine-scanning mutagenesis, either as a series of separately synthesized single substitution mutants, or in one fell swoop by combinatorial Ala-scanning mutagenesis. The skilled worker could choose not to further mutate an Ala-intolerant position.

The determination of the arylsulfatase A activity of any mutant is straightforward, see page 13, lines 21-29:

> "an amino acid sequence or a portion of an amino acid sequence is a polypeptide capable of hydrolysing an amount of the arylsulfatase A substrate pNCS at 37°C a rate corresponding to a specific activity of at least 20 U/mg polypeptide (preferably 50 U/mg polypeptide) when determined in an assay for measuring arylsulfatase A activity as described in example 1 of the present application, and/or a polypeptide, which is capable of hydrolysing at least 40% of labelled arylsulfatase A substrate, fx. ^{14}C palmitoyl sulfatide, loaded into MLD fibroblasts, when assayed by incubation at a dose level of 25 mU/ml in an assay as described in example 2 of the present invention".

The skilled worker may confine mutation to the non-conserved residues of the arylsulfatases.

The skilled worker may further limit early experimentation to the conservative substitution mutants generally recognized in the art, e.g., exchange of Leu and Ile. While the specification does not explicitly recite a list of conservative substitution exchange groups, it discloses sequence alignment using the scoring matrix of Gonnet (P16, L5). Such a matrix scores amino acid pairs, with a maximum value given to identities, and a lesser value given to mismatches, but with similar amino acids scoring higher than dissimilar ones. Thus, by studying the values in the matrix, one can infer a ranking of possible replacements.

Each mutant tested would of course provide information which

would guide further experimentation.

Thus, based on the above the skilled person will, without undue burden, be able to determine the specific activity of selected amino acid sequences - i.e. to identify members of the rhASA genus. We respectfully submit that a limitation to a specific amino acid sequence will leave applicant with an unreasonable limited scope of protection as 3rd parties would be able to take unreasonably advantage of the teaching of the present invention, knowing these sequences may easily be modified in order to work around the claims as long as the sequence includes the necessary catalytic site to exert substantially the same enzymatic activity as the full length enzyme.

Should the examiner not be persuaded that amended claim 1 satisfies the enablement requirement, separate consideration should be given to new claims 43-59.

6. Prior Art Rejections - 35 USC § 102

Claims 1-2, 7-9, 11-16 and 18 have been rejected under 35 USC § 102 (b) as being anticipated by Fogh et al. (WO 02/098455).

We respectfully traverse this rejection. Fogh et al. discloses a process for the production of rhASA in a semi-large scale fermentation comprising culturing a CHO-ASA cell line in a 5 liter bioreactor followed by a purification process comprising several steps of ion exchange chromatography (Examples 5 and 6). The subject matter of claim 1 therefore differs from this known process in that the production occurs in a continuous process, whereas the process of the Fogh et al. reference is a batch process (see P37, L25; "2 batches were produced").

As noted by the specification at P17, L1-4:

> One immediate advantage of this system as compared to a batch system is to allow for an effective production phase extending over longer time. It is therefore within the scope of the present invention to operate the system continuously over a period

> extending over one week, preferably two weeks, more preferably 3 weeks, even more preferably 4 weeks.

See new claim 42.

Furthermore the Fogh et al. reference does not disclose a polishing step including a passive step, wherein the arylsulfatase A passes through a cation exchange chromatography resin or membrane and/or affinity chromatography resin. To the contrary the Fogh et al. reference merely discloses an active step[3]. Thus, the reference describes polishing steps at page 42 (step 5). Three different options are given:

1) hydroxyapatite (per the reference to step 4, there is elution with 75% buffer A=25% buffer B, buffer A is Tris-HCl and B is sodium phosphate.)
2) anion exchange with salt gradient elution
3) cation exchange with salt gradient elution.

All of these appear to be active steps.

In the present disclosure, page 59, the polishing step combines a passive step (passage through Mustang-S or Blue Sepharose membrane) with an active step (anion exchange). (The claim generalizes the passive step by replacing Mustang-S with "cation exchange chromatography resin or membrane" and Blue Sepharose with "affinity chromatography resin".)

We direct the examiner's attention to P18, L29-P19, L2:

> Furthermore it is preferred that the concentration and purification process of (ii) comprises a polishing step including a passive step, wherein the arylsulfatase A passes through an affinity chromatography resin or membrane and/or a cation chromatography resin or membrane, and an active step, wherein the arylsulfatase A is detained within and subsequently eluted from an anion exchange membrane or resin. This combination of passive and active steps is

[3] In a passive step, the rASA merely (selectively) passes through the membrane, whereas in an active step, it is retained and then (selectively) eluted, see P25, L12-16.

> suggested from the surprising finding that whereas most contaminating proteins binds to an anion exchange matrix at pH values less than 5.8, preferably at pH values around 5.5-5.7, arylsulfatase A will pass the cation exchange matrix and subsequently bind to an anion exchange resin. It is believed that a change in the structure of the enzyme from a dimer to an octamer at pH values below 5.8 is responsible for this surprising effect. This change in structure has physiological relevance since the enzyme is active in the lysosomes at low pH.

Thus, based on the above the Examiner should withdraw the rejection under 35 USC § 102 (b).

7. Conclusion

The Examiner is respectfully requested to reconsider and withdraw the objections and rejections, and to pass the claims of the present application to issue.

Respectfully submitted,

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